## REMARKS

Claims 1-6 are pending, claims 7-8 being canceled pursuant to the restriction requirement. Support for the amendments to the claims, which are formal in nature, is replete throughout the specification as filed. No new matter is introduced by the amendments.

Claims 1-6 were rejected for alleged lack of written description, enablement, clarity and anticipation. To the extent that the rejections are applied to the amended claims, Applicants traverse.

PRIORITY

The Examiner noted that the priority claim to 60/433,045 was not present in the first sentence of the application, although priority was properly claimed in the PCT and in Applicants' declaration. Applicants have corrected this formal requirement by amending the specification to reflect the priority claim of record. Accordingly, Applicants are entitled to priority to USSN 60/433,045.

DRAWINGS

The drawings were rejected because the description for Figure 1 referred to color features of the black and white drawing. The specification has been amended to better correspond to the drawing, which has also been clarified for black and white presentation. The Objection should be withdrawn.

Figure 2 was objected to for not using SEQ ID NOs. The brief description has been amended to reflect SEQ ID NOs. of the drawing, and a formal sequence listing accompanies this Amendment. The Objection should be withdrawn.

SEQUENCE RULES

The specification and drawings were objected to as lacking a formal sequence listing. A formal sequence listing accompanies this amendment. The Objection should be withdrawn.

INFORMATION DISCLOSURE STATEMENT

The reference lists in the specification are indicated not to be formal IDS. Applicants enclose herewith an appropriate IDS.

REJECTION FOR LACK OF WRITTEN DESCRIPTION

The Action argues that the application fails to provide an adequate written description of markers within a block of linkage disequilibrium surrounding the DRD47R allele. Applicants traverse.

It appears that the crux of the rejection may be based partly upon a technical misunderstanding of the data presented. Specifically, the Action argues that insufficient members of the claimed genus are provided, and states that "This large genus is represented in the specification by only a single named polymorphism, namely the repeat polymorphism in exon 3, DRD4-7R."

The difficulty with this argument is that it is *completely* wrong on a technical level. The Examiner is referred, e.g., to page 8 and Figure 2 of the application. **600** chromosomes were sequenced in the region surrounding DRD4. **56** different haplotypes were found. Of the 56 different haplotypes, ***35 distinct DRD4-7R alleles were identified!***

**Thus, just with reference to the DRD4-7R repeat type in question, Applicants identified 35 different alleles displaying the 48 bp "7R" motif. The application, thus, provides at least 35 different working examples of haplotypes that meet the limitations of the claims.**

Applicants have more than demonstrated that these 35 different haplotypes are representative, because of the very large sample size (600 chromosomes!) that was sampled and because the samples themselves were selected to maximize the representative diversity of the samples at issue (See page 6; the samples were carefully selected from North and South America, Europe, Asia, Africa, and the Pacific region; note that the samples were also intentionally oversampled with respect to ADHD patients).

Finally, it is worth noting that one of the *surprising* findings by the inventors was that the haplotypes display extremely strong linkage disequilibrium between polymorphisms of the haplotype of the 7R region, presumably because the 7R allele type is a recent evolutionary development. See Application, pages 11-12. Thus, polymorphisms closely linked to a particular 7R allele are *extremely* predictive of that particular allele.

There are few-- if any-- similar examples in the literature, where so many haplotypes have been identified for a particular genomic region, following such a thorough representative sampling protocol. In point of fact, it is unusually clear that Applicants have met written description in the present case, in that a large and plainly representative sample was analyzed to identify *many* different 7R haplotypes. In the final analysis, Applicants have met the written description requirement in the current case in precisely the manner the Courts have articulated to be most appropriate, i.e., "through sufficient description of a representative number of species" as well as "by

actual reduction to practice" as well as "by disclosure of relevant, identifying characteristics." MPEP 2163 at 2100-174.

The rejection must be withdrawn.

REJECTION FOR LACK OF ENABLMENT

The Action alleged that claims 1-6 are not enabled, because the art is unpredictable. Applicants traverse.

The Action alleges that the invention fails to meet the enablement standard articulated by In Re Wands 8USPQ2nd 1400 (Fed Cir 1988). As identified by the Examiner, the Wands case sets forth a classic multi-part analysis to be used for determining whether undue experimentation is required in practicing a claimed invention. In understanding how each of the features of this analysis should be applied to the present case, it is instructive to examine the facts and holdings of Wands, to understand how the facts of the present case can be compared to the Wands case and how these facts fit into the framework of the Wands analysis. As will be shown in detail below, it is plain that the present invention more than meets the requirements to provide enablement as articulated by Wands.

The claim at issue in Wands was an immunoassay method claim with two steps: first, a test sample containing a hepatitis B-surface antigen was contacted with an antibody, and second, the resulting substance was detected (using the antibody). The antibody was specified as having a binding constant of $10^9$ /M. The Patent Office argued that the production of high affinity antibodies was unpredictable, and, therefore, that undue experimentation would have been required to practice the invention. The Court disagreed and struck down the PTO's rejection, setting forth a framework for the analysis to be followed by the Office in the future when assessing whether undue experimentation is required in the practice of the invention.

**Wands Factor 1—The Quantity of Experimentation is reasonable and is no more than was the case in Wands**

The first factor identified by the Court was "(1) the quantity of experimentation necessary" to practice the claimed invention. In its analysis, the Court first noted that the experimental process for making antibodies that bound the relevant antigen were set forth in the application. In essence, this process included an elaborate hybridoma fusion screening and manipulation procedure, followed by a binding screen to identify "high binders" followed by another screening procedure to identify what type of antibody had been generated (IgM being the desirable antibody type in Wands). The PTO argued that less than 3% of hybridomas that were created

produced antibodies, and of these, only 20% produced IgM antibodies. The first four hybridoma fusion experiments performed by the Wands inventors were failures, with the next 6 being successful. The Court held that this was not evidence of unpredictability, particularly given that the technique at issue was in general use for antibody production. Wands at 1406.

The same essential logic as was applied by the Wands Court applies to the facts at hand. In Wands, there was no unpredictability in performing the method itself, i.e., antibody detection of antigens was well known. Here, there is no unpredictability in *performing* the claimed method, i.e., detection of nucleic acid polymorphisms is routine (and expressly taught) and the detection of dopamine release, while slightly more complex than simple genetic screening, is also an available method that is well taught in the application (see pages 18-24). That is, there is **no** experimentation, at all, required to either test for genetic polymorphisms in DRD4, or to test for dopamine release. The issue raised by the Examiner is whether the tests have any relevance to ADHD, e.g., whether DRD4-7R really correlates with ADHD, or whether dopamine release has any relevance to an ADHD phenotype.

With respect to the genetic association study, the Examiner calls into question the idea of whether *any* genetic correlation study can be correlated to a phenotype, citing Hirschhorn. Applicants respectfully submit that this argument is not persuasive. There are dozens of genetic tests that are well accepted in the medical and scientific community. The fact that some initial associations are lost when larger confirmatory studies are performed is not an indictment of the idea of genetic testing; instead, it is an indication that sufficient statistical certainty has to be developed by confirmatory testing before any meaningful genetic test can be designed. In the present case, the ADHD/DRD4-7R correlation analysis that was performed *is* the confirmatory expanded testing that provides additional statistical information to prove the correlation. Prior to the substantially expanded study presented in the application, smaller scale studies were in disagreement as to the essential relevance of the 7R allele, with some studies finding a lack of association (see, e.g., Castellanos et al., 1998; IDS reference), while others found a correlation between ADHD and the DRD47R allele (La Hoste et al. 1996; Swanson et al. 1998).

Moreover, the specific issues raised by Hirschhorn and specifically referenced by the Examiner are actually addressed in the present invention. As has already been described, the samples at issue were broadly selected and did not display population stratification, the first concern raised by the Examiner (i.e., as Applicants demonstrated, the 7R allele is statistically well-correlated with ADHD in populations from North and South America, Asia, Pacifica, and Africa). As has already been mentioned with respect to the second issue, possible linkage disequilibrium, the haplotypes at

issue rather unusually display minimal linkage disequilibrium in the region at issue—virtually every sample in the large sample set shows *complete* linkage through the 7R region. The gene at issue, the DRD47R displays very strong genetic effects, i.e., it appears to be the *main* genetic contributor to the genetic predisposition to ADHD, rather than simply being a minor or nominal contributor.

It is also, of course, true that the results of testing have to be analyzed meaningfully. As the inventors note (page 5), "As in all association studies, however, one can not assume that the presence of a DRD4 7R-allele is either necessary or sufficient to "cause" ADHD." Indeed, it is plain that there are environmental factors (especially minimal brain damage) that lead to "true" ADHD even in individuals that do *not* have the 7R allele, and, contrawise, that many individuals with the allele do not display any clear ADHD symptoms (and those symptoms that are displayed relate to behavioral phenotypes, rather than to cognitive deficit phenotypes; see specification, page 4).

Indeed, one of the reasons the genetic correlation is interesting is that the 7R risk allele can produce many of the *behavioral* symptoms of ADHD, without the long term *cognitive* deficits that characterize more severe forms of ADHD (see Application at page 4). Abnormal dopamine release is a marker for "true" ADHD; thus, children that display a normal release of dopamine, but also have the 7R allele are likely to "grow out of" many of the ADHD symptoms. Thus, a diagnosis of DRD4 7R in a child displaying ADHD symptoms without cognitive deficits and without a dopamine release abnormality may actually be a positive finding, as many such patients that do not display cognitive deficits can become more productive with maturity.

**Wands Factor 2: The Direction or Guidance Provided is Extensive**

The second factor identified by Wands was the amount of direction or guidance presented. The Wands court indicated that the Wands specification provided considerable guidance, and presented working examples.

In the present case *far more* guidance is provided than in Wands. Specifically, 35 different working examples of DRD4 7R haplotypes are provided (in comparison to the 3 working examples in Wands!). In addition, about 20 patients were analyzed for dopamine release, providing a further 20 working examples of this step of the methods. Thus, not only have applicants provided working examples, they have actually provided extensive working examples.

The Examiner's main concern with respect to the guidance presented is an argument that the 7R allele status of the patients evaluated for Dopamine release was not indicated. This is not actually the point of the dopamine release studies, which were designed to confirm the dopamine hypothesis that derives from the clinical use of CA agonists to treat ADHD. The exercise study confirmed the dopamine hypothesis (application at page 24).

**Wands Factor 3: Dozens of Working Examples Are Provided**

The third factor identified by Wands is ultimately a restatement of part of the second factor, i.e., the presence or absence of working examples. As has been detailed, Applicants have more than met their burden in this regard, with many "past tense" working examples falling within the claims having been expressly taught Obviously, this provides far more detail with respect to working examples than the Wands disclosure of, at most, four working embodiments (three or four antibodies with some activity, depending on what part of the Wands decision one reviews).

**Wands Factor 4: The Nature of the Invention**

The fourth factor identified by the Wands court is the "nature of the invention." Wands indicates that, "the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners in this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." Wands at 1406. The Office alleged that the success rate of such screening for antibodies was just 2.8%, which the Court largely disagreed with, but also indicated that even such a low success rate would not lead to a conclusion of undue experimentation, because any experimentation was of the type expected in the art. Wands Fn 29.

In this respect, the nature of the art for the subject application is closely analogous to Wands. The field includes genetic and behavioral testing and psychiatric evaluation. One of skill in the art is certainly prepared to do genetic and dopamine screening in evaluating and analyzing a patient that displays signs of ADHD. Indeed, it may fairly be said that such molecular screening is far easier to perform, and produces a more concrete result, than the cognitive and behavioral evaluations that are already part of an ADHD diagnosis.

**Wands Factor 5: The State of the Prior Art**

The fifth factor identified by the Wands court is the state of the prior art. Wands indicated that the state of the prior art was advanced, with "all of the methods required to practice the invention being known." This is precisely true for the present case as well. Every step used to practice the method can be practiced using available technology for testing for polymorphisms and, e.g., dopamine release. Indeed, given that Wands was decided in 1988, it is also plain that the state of the relevant prior art is enormously *more* advanced than it was in 1988. The pace of technological innovation in biotechnology over the 20 years since the Wands decision (and 25+ years since the underlying Wands application) makes the methods and techniques available to one of skill at the time

of that decision seem rather quaint. In any case, as with the techniques used by Wands, the basic underlying molecular biological technique used in the present invention are, plainly, well known.

**Wands Factor 6: The relative Skill of Practitioners in the Field**

The sixth factor identified by Wands is the relative skill of practitioners in the field. The level of skill of practitioners in the field was considered "high" for the Wands decision. Obviously, it is much higher now than it was in the early to mid 1980s. The information that practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical postdoctoral researcher or principal investigator can, for example, sequence and provide a detailed analysis of thousands of biological samples in a matter of hours, whereas in the 1980s, a week could go by to get one simple sequencing reaction to work, due to the extensive manual manipulations that had to be performed. Anyone who is mature enough in the field to remember manually pouring sequencing gels, by manually assembling massive glass plates, taping them together, mixing acrylamide, tapping the glass for minutes to remove bubbles, only to end up breaking the glass and starting over again—the next day, because the pouring of the gel and running of the sequencing reaction, by hand, took all day—will immediately appreciate the dramatic changes that have taken place in, e.g., genetic screening. If the level of skill in the art was "high" at the time of Wands then it is now positively stratospheric. In any case, any moderately competent molecular biologist (or, lab technician), given Applicants' disclosure can certainly routinely perform each and every step required to practice the claimed methods.

**Wands Factor 7: The Predictability or Unpredictability of the Art**

The seventh factor identified by Wands is the unpredictability of the art. In Wands, the Patent Office had argued that the "low" observed 2.8% rate of success in screening for antibodies in the case was evidence of unpredictability. However, the Court took a different view, noting that in several of the cases in which an entire overall antibody production screen was performed, at least one antibody was produced. In the present case, in the many working examples provided, various correlations between ADHD and dopamine and the DRD47R allele were, plainly, established.

The Examiner raises several issues with regard to predictability, including gender specific reactions of boys and girls diagnosed with ADHD to exercise, and failure in the treatment of ADHD through Yoga. The difficulty with the arguments raised are that they are irrelevant to the *claimed* invention. Applicants have not claimed a method for *treating* ADHD through exercise. The cited art has no clear relevance to the issue of ADHD *testing*.

The rejection's comments regarding the association of genes and phenotypes is addressed under Wands Factor 1, and, in the interest of concise argument, is not readdressed here.

The rejection also essentially argues that biotechnology is unpredictable, citing Mycogen v. Monsanto 243 F. 3d 1316, 1330 (Fed Cir. 2001). The Examiner is respectfully reminded that the Mycogen case was one in which the issue with respect to unpredictability was the issue of *conception* of the invention. As the Court noted, in an unpredictable art, conception and reduction to practice are said to be "simultaneous." The Court did not say, and has never said, that an invention, *once reduced to practice*, cannot be enabled because the art that the invention is in is unpredictable. While unpredictability certainly can be used to establish lack of expectation of success in an *obviousness* context, or in determining a date of completed *conception*, once reduced to practice, an invention becomes rather more predictable. In the present case, there is no unpredictability in the *claimed method*, i.e., knowing the genetic status of the DRD4 locus and the level of dopamine release in response to a stimulus provides useful information to the clinician in the diagnosis of the various forms of ADHD noted in the application.

**Wands Factors Conclusions**

In each and every case, comparison of the current invention to the facts of the seminal Wands decision shows that Applicants have provided more than was the case in Wands, that the art is more advanced than was the case in Wands, that people are far more skilled than was the case in Wands, that there is no more unpredictability than was the case in Wands and that far more working examples are provided than was the case in Wands. Accordingly, each and every factor in the balancing test specified by the Federal Circuit mitigates *in favor* of Applicants. The rejection must be withdrawn.

REJECTION UNDER 35 USC § 112, PARA. 2

Claims 1-6 were rejected for alleged failure to point out and claim the invention.

Specifically, the Examiner noted a lack of correlation between the preamble and the body of claim 1. Claim 1 has been amended to more clearly relate the preamble and method steps. Accordingly, the rejection should be withdrawn.

Claim 6 was further rejected for use of the phrase "corresponds to." Applicants have amended the claim with the more traditional phrase "comprising." The rejection should be withdrawn.

REJECTION FOR ANTICIPATION

Claims 1-6 are rejected for alleged anticipation by Wigal (2003). Applicants traverse.

Applicants have perfected their priority claim to 60/433,045. Accordingly, Wigal is not prior art. The rejection must be withdrawn.

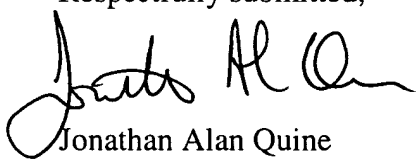
## CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

QUINE INTELLECTUAL PROPERTY LAW GROUP
P.O. BOX 458, Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877
PTO Customer No.: **22798**
Deposit Account No.: **50-0893**

Respectfully submitted,



Jonathan Alan Quine
Reg. No: 41,261

Attachments:

1) A petition to extend the period of response for **3** months;
2) A transmittal sheet;
3) A fee transmittal sheet;
4) Replacement Drawing Sheet;
5) Statement Accompanying Sequence Listing;
6) Paper copy of Sequence Listing;
7) CD;
8) Information Disclosure Statement;
9) PTO-1449 Form;
10) 16 References;
11) A copy of the PCT Search Report; and,
12) A receipt indication postcard.